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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/341,641	09/09/1999	GUNTER SCHMIDT	020600-280	5378

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EXAMINER
CHAKRABARTI, ARUN K

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1634	20

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/341,641	Schmidt et al.
Examiner	**Art Unit**
Arun Chakrabarti	1655

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- *Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.*
- *If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.*
- *If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.*
- *Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).*
- *Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).*

Status

1) ☒ *Responsive to communication(s) filed on* Jan 23, 2002 .

2a) ☐ *This action is* **FINAL.** 2b) ☒ *This action is non-final.*

3) ☐ *Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.*

Disposition of Claims

4) ☒ *Claim(s)* 21-39 and 41-43 *is/are pending in the application.*

4a) *Of the above, claim(s)* _____ *is/are withdrawn from consideration.*

5) ☐ *Claim(s)* _____ *is/are allowed.*

6) ☒ *Claim(s)* 21-39 and 41-43 *is/are rejected.*

7) ☐ *Claim(s)* _____ *is/are objected to.*

8) ☐ *Claims* _____ *are subject to restriction and/or election requirement.*

Application Papers

9) ☐ *The specification is objected to by the Examiner.*

10) ☐ *The drawing(s) filed on* _____ *is/are objected to by the Examiner.*

11) ☐ *The proposed drawing correction filed on* _____ *is: a)* ☐ *approved b)* ☐ *disapproved.*

12) ☐ *The oath or declaration is objected to by the Examiner.*

Priority under 35 U.S.C. § 119

13) ☐ *Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).*

a) ☐ *All* b) ☐ *Some** c) ☐ *None of:*

1. ☐ *Certified copies of the priority documents have been received.*
2. ☐ *Certified copies of the priority documents have been received in Application No.* _____ .
3. ☐ *Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).*

**See the attached detailed Office action for a list of the certified copies not received.*

14) ☐ *Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).*

Attachment(s)

15) ☐ *Notice of References Cited (PTO-892)*

16) ☐ *Notice of Draftsperson's Patent Drawing Review (PTO-948)*

17) ☐ *Information Disclosure Statement(s) (PTO-1449) Paper No(s).* _____

18) ☐ *Interview Summary (PTO-413) Paper No(s).* _____

19) ☐ *Notice of Informal Patent Application (PTO-152)*

20) ☐ *Other:*

DETAILED ACTION

Request for Continued Examination

1. A request for continued examination under 37 CAR 1.114, including the fee set forth in 37 CAR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CAR 1.114, and the fee set forth in 37 CAR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CAR 1.114. Applicant's submission filed on January 23, 2002 has been entered.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CAR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made

in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

3. Claims 21-32 are rejected under 35 U.S.C. 103 (a) over Southern et al. (PCT International Publication Number: WO 95/04160) (February 9, 1995) in view of Bensimon et al. (U.S. Patent 5,866,328) (February 2, 1999).

Southern et al. teaches a method for sequencing DNA (Abstract with Figure), which comprises:

(a) obtaining a target DNA population comprising a plurality of single-stranded DNAs to be sequenced, each of which is inherently present in a unique amount in the same reaction zone and bears a primer to provide a double-stranded portion of the DNA for ligation thereto (Figure 5 and Example 16 b, lines 1-12 and Claims 16 a and 16 b);

(b) contacting the DNA population with an array of hybridization probes, each probe comprising a label cleavably attached to a known base sequence of predetermined length, the array containing all possible base sequences of that predetermined length and the base sequence being incapable of ligation to each other, wherein the contacting is carried out in the presence of ligase under conditions to ligate to the double-stranded portion of each DNA the probe bearing the base sequence complementary to the single-stranded DNA adjacent the double-stranded portion thereby to form an extended double-stranded portion which is incapable of ligation to further probes (Figures 4 and 5 and Claims 16 a to 16 d and Claims 20 a to 20 d);

c) removing all unligated probes (Claims 16 e and 20 e); followed by the steps of :

(d) cleaving the ligated probes to release each label (Figures 3a, 3b and 4, and Page 16, lines 5-18 and Example 18);

(e) recording the quantity of each label (Example 19, Figures 3b, 4 and 5 and claims 16 f and 20 f); and

(f) activating the extended double-stranded portion to enable ligation thereto (Page 16, lines 15-18, Figures 4 and 5);

(g) steps (b) to (f) are repeated in a cycle for a sufficient number of times to determine the sequence of each single-stranded DNA by determining the sequence of release of each label (Figure 4 and page 16, lines 19-26 and claim 17).

Southern et al. teaches a method wherein the array comprises a plurality of sub-arrays which together contains all possible base sequences (Page 17, line 1 to page 18, line 5 and page 19, line 26 to page 21, lines 23 and claim 20).

Southern et al. teaches a method wherein the initial DNA sample is cut into fragments, each having a sticky end of known length and unknown sequence, which fragments are sorted into subpopulations according to their sticky end sequence (Example 16 b).

Southern et al. teaches a method wherein each single-stranded DNA is immobilized at one end (Figures 4 and 5).

Southern et al. teaches a method wherein the label of each probe comprises a mass label, and the quantity of each label is recorded using mass spectrometry after release of the label (Example 19).

Southern et al. teaches a method wherein the known base sequence is blocked at its 3' OH (Figure 4, step 1).

Southern et al. teaches a method wherein the step of cleaving the ligated probes to release each label unblocks the 3' -OH of the extended double-stranded portion (Figure 4, step 2).

Southern et al. teaches a method wherein the label of each probe is cleavably attached to the 3'-OH of the base sequence (Figure 4).

Southern et al. teaches a method wherein the base sequence of each probe is unphosphorylated at both 3' and 5' ends and comprises phosphorylating the 5'-OH of the extended double-stranded position (Figure 4, steps 3 and 4).

Southern et al. teaches a method wherein the predetermined length of the base sequence is from 2 to 6 (Page 2, lines 2-8).

Southern et al does not teach a method wherein a heterogeneous population of single-stranded DNA is immobilized in a unique amount in the same reaction zone.

Bensimon et al. teaches a method wherein a heterogeneous population of single-stranded DNA is immobilized in a unique amount in the same reaction zone (Column 7, line 16 to column 8, line 67).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to substitute and combine the heterogeneous population of single-stranded DNA immobilized in a unique amount in the same reaction zone of Bensimon et al in the assay method of Southern et al. since Bensimon et al. states, "This method enables a heterogeneous population

of DNA molecules (already anchored to the movable support) to be sequenced or tested in series (Column 7, lines 27-29)". By employing scientific reasoning and in order to improve the sequencing of heterogeneous population of DNA molecules, an ordinary practitioner would have been motivated to substitute and combine the heterogeneous population of single-stranded DNA immobilized in a unique amount in the same reaction zone of Bensimon et al in the assay method of Southern et al. In order to achieve the express advantages, as noted by Bensimon et al, of a method which enables a heterogeneous population of DNA molecules (already anchored to the movable support) to be sequenced or tested in series.

4. Claims 21-25 and 27-32 are rejected under 35 U.S.C. 103 (a) over Macevicz et al. (PCT International Publication Number: WO 96/33205) (October 24, 1996) in view of Bensimon et al. (U.S. Patent 5,866,328) (February 2, 1999).

Macevicz et al. teaches a method for sequencing DNA (Abstract with Figure), which comprises:

(a) obtaining a target DNA population comprising a plurality of single-stranded DNAs to be sequenced, each of which is inherently present in a unique amount in the same reaction zone and bears a primer to provide a double-stranded portion of the DNA for ligation thereto(Figure 1 and page 10, lines 16 to page 11, lines 23);

(b) contacting the DNA population with an array of hybridization probes, each probe comprising a label cleavably attached to a known base sequence of predetermined length, the array containing all possible base sequences of that predetermined length and the base sequence being

incapable of ligation to each other, wherein the contacting is carried out in the presence of ligase under conditions to ligate to the double-stranded portion of each DNA the probe bearing the base sequence complementary to the single-stranded DNA adjacent the double-stranded portion thereby to form an extended double-stranded portion which is incapable of ligation to further probes (Figures 1-4 and Claim 13);

c) removing all unligated probes (Claim 13); followed by the steps of :

(d) cleaving the ligated probes to release each label (Figures 1-4);

(e) recording the quantity of each label (Example 1, page 21, lines 19-27); and

(f) activating the extended double-stranded portion to enable ligation thereto (Figures 1-4 and Example 1, page 21, last paragraph);

(g) steps (b) to (f) are repeated in a cycle for a sufficient number of times to determine the sequence of each single-stranded DNA by determining the sequence of release of each label (Figures 1-4 and Example 1, page 21, last paragraph).

Macevicz et al. teaches a method wherein the array comprises a plurality of sub-arrays which together contains all possible base sequences (Example 1).

Macevicz et al. teaches a method wherein the initial DNA sample is cut into fragments, each having a sticky end of known length and unknown sequence, which fragments are sorted into subpopulations according to their sticky end sequence (page 5, line 25 to page 6, line 18).

Macevicz et al. teaches a method wherein each single-stranded DNA is immobilized at one end (Figures 1-4).

Macevicz et al. teaches a method wherein the known base sequence is blocked at its 3' OH (Figure 4, step 2).

Macevicz et al. teaches a method wherein the step of cleaving the ligated probes to release each label unblocks the 3' -OH of the extended double-stranded portion (Figure 4, step 3).

Macevicz et al. teaches a method wherein the label of each probe is cleavably attached to the 3'-OH of the base sequence (Figure 4, steps 4 and 5).

Macevicz et al. teaches a method wherein the base sequence of each probe is unphosphorylated at both 3' and 5' ends and comprises phosphorylating the 5'-OH of the extended double-stranded position (Figures 2 and 3b).

Macevicz et al. teaches a method wherein the predetermined length of the base sequence is from 2 to 6 (Page 7, lines 7-20).

Macevicz et al does not teach a method wherein a heterogeneous population of single-stranded DNA is immobilized in a unique amount in the same reaction zone.

Bensimon et al. teaches a method wherein a heterogeneous population of single-stranded DNA is immobilized in a unique amount in the same reaction zone (Column 7, line 16 to column 8, line 67).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to substitute and combine the heterogeneous population of single-stranded DNA immobilized in a unique amount in the same reaction zone of Bensimon et al in the assay method of Macevicz et al. since Bensimon et al. states, "This method enables a heterogeneous population

of DNA molecules (already anchored to the movable support) to be sequenced or tested in series (Column 7, lines 27-29)". By employing scientific reasoning and in order to improve the sequencing of heterogeneous population of DNA molecules, an ordinary practitioner would have been motivated to substitute and combine the heterogeneous population of single-stranded DNA immobilized in a unique amount in the same reaction zone of Bensimon et al in the assay method of Macevicz et al in order to achieve the express advantages, as noted by Bensimon et al, of a method which enables a heterogeneous population of DNA molecules (already anchored to the movable support) to be sequenced or tested in series.

5. Claims 21-39 and 41-43 are rejected under 35 U.S.C. 103 (a) as being unpatentable over Southern et al. (PCT International Publication Number: WO 95/04160) (February 9, 1995) in view of Bensimon et al. (U.S. Patent 5,866,328) (February 2, 1999) further in view of Stratagene Catalog (1988, page 39).

Southern et al in view of Bensimon et al. teaches the method of claims of 21-32 including array of hybridization probes comprising mass labels as described above.

Southern et al in view of Bensimon et al. do not teach the motivation to combine all the reagents for identifying a base at a target position in a single-stranded sample DNA sequence in the form of a kit.

Stratagene catalog teaches a motivation to combine reagents into kit format (page 39).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine all the reagents e.g., array of hybridization probes comprising mass

labels etc. of Southern et al in view of Bensimon et al into a kit format as discussed by Stratagene catalog since the Stratagene catalog teaches a motivation for combining reagents of use in an assay into a kit, "Each kit provides two services: 1) a variety of different reagents have been assembled and pre-mixed specifically for a defined set of experiments. Thus one need not purchase gram quantities of 10 different reagents, each of which is needed in only microgram amounts, when beginning a series of experiments. When one considers all of the unused chemicals that typically accumulate in weighing rooms, desiccators, and freezers, one quickly realizes that it is actually far more expensive for a small number of users to prepare most buffer solutions from the basic reagents. Stratagene provides only the quantities you will actually need, premixed and tested. In actuality, the kit format saves money and resources for everyone by dramatically reducing waste. 2) The other service provided in a kit is quality control". (page 39, column 1).

Response to Arguments

6. Applicant's arguments filed on January 23, 2002 have been fully considered but they are not persuasive.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicant argues that there is no motivation to combine the references. This argument is not persuasive, especially in the presence of strong motivation provided by Bensimon et al. since Bensimon et al. states, "This method enables a heterogeneous population of DNA molecules (already anchored to the movable support) to be sequenced or tested in series (Column 7, lines 27-29)".

In response to applicant's argument that Bensimon et al reference motivates only the advantage of atomic force microscopy and not the advantage of an independent feature of immobilizing a heterogeneous population of DNAs on solid support, the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985).

Applicant argues that Bensimon et al reference does not teach the "single stranded DNA" of the claimed invention. Applicant argues that the word "single stranded DNA" was not found in Bensimon reference and only the word "double stranded DNA" is found. Applicant argues that because Bensimon has a preferred embodiment of "double stranded DNA", Bensimon is limited to the preferred embodiment. This argument is not persuasive. As MPEP 2123 states "Disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments. In re Susi,169 USPQ 423 (CCPA 1971)." MPEP 2123 also states " A reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill the art, including nonpreferred embodiments. Merck & Co. v. Biocraft Laboratories , 10 USPQ2d 1843 (Fed. Cir. 1989)." It is clear that simply because Skiena has a preferred

embodiment, this embodiment does not prevent the reference from suggesting broader embodiments in the disclosure and that this does not constitute a teaching away. Although Bensimon reference uses the word "double stranded DNA", the property of "single stranded DNA" is also measured by Bensimon. For example, Bensimon teaches that such "single stranded DNA" can be produced from a "double stranded DNA", (Column 7, lines 45-47 and Figure 2a). Moreover, MPEP 2111 states, "Claims must be given their broadest reasonable interpretation. During patent examination, the pending claims must be "given the broadest reasonable interpretation consistent with the specification". Applicant always has the opportunity to amend the claims during prosecution and broad interpretation by the examiner reduces the possibility that the claim, once issued, will be interpreted more broadly than it is justified. *In re Prater,* 415 F.2d 1393, 1404-05, 162 USPQ 541, 550-51 (CCPA 1969)". In this case, any "single stranded DNA" under any suitable conditions (no matter it is originally present or derived from a double stranded DNA, especially in the presence of "comprising" language of the claim) can be used for estimating the sequence of nucleic acids.

Conclusion

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Arun Chakrabarti, Ph.D. whose telephone number is (703) 306-5818. The examiner can normally be reached on 7:00 AM-4:30 PM from Monday to Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax phone number for this Group is (703) 305-7401.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Arun Kr. Chakrabarti

Arun Chakrabarti,

Patent Examiner,

February 5, 2002